Indian Journal of Fundamental and Applied Life Sciences ISSN: 2231-6345 (Online)
An Online International Journal Available at http://www.cibtech.org/jls.htm
2012 Vol. 2 (2) April-June, pp.269-275/Duhan et al.
Research Article

INTRACERVICAL DINOPROSTONE VERSUS VAGINAL ISOSORBIDE DINITRATE FOR CERVICAL RIPENING AT TERM

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ABSTRACT
Favourability of cervix is important for successful induction of labor. Various methods to ripen the cervix have been tried with variable success and limitations. The aims of present study were to evaluate the role of Isosorbide dinitrate (IDN) as cervical ripening agent and to analyse its efficacy and safety in comparison to dinoprostone gel. Prospective randomized controlled trial. One hundred primigravid women posted for induction of labor between Jan 2006 to 2008 with singleton pregnancy between 37 to 42 weeks and with a modified Bishop score of 5 or less were randomized to receive either IDN 40mg vaginally (group I) or dinoprostone gel 0.5 mg intracervically (group II) in this prospective study at a tertiary care centre of India. After an informed consent, women of group I were administered. 40 mg IDN as vaginal tablet while group II received dinoprostone gel (0.5 mg) intracervically. The dinoprostone gel instillation was repeated after 6 hours if the Bishop score remained poor. Oxytocin started after 12 hours in both groups if required. Primary outcomes were change in bishop score, time from induction to delivery and maternal and fetal adverse effects. Secondary outcome included cesarean section rate, deliveries within 12 and 24 hours of entry and oxytocin requirement and dose into the study. All women were monitored for pulse rate, blood pressure, fetal heart rate, uterine contractions, adverse effects and maternal and neonatal outcome. Chi square test with $p < 0.05$ being considered significant. The mean bishop score was 3.44±1.23 in group I and 3.20±1.19 in group II and the change by the score after 6 hours of administration of the ripening agent in both groups was significant ($p<0.001$). Nine and 13 women of group I and group II, respectively delivered within 12 hours of entry while the respective values after 24 hours were 38 and 31. The mean induction to delivery internal was 17.99±7.05 hours in group I and 16.68±3.47 hours in group II ($p>0.05$). Oxytocin was required in 38 women of group I and 33 of group II of which 22 from group I and 14 from group II required >20 mIU/min of oxytocin ($p>0.05$). Cesarean section was required in 7 and 12 women of Group I and II respectively. Fetal distress accounted for 11 out of 12 cesarean sections in group II, against 4 out of 7 in group I. A higher incidence of headache was observed in group I while uterine tachysystole and abnormal fetal heart rate patterns were more frequent with dinoprostone. Though comparable in efficacy to dinoprostone for cervical ripening, IDN, a cost effective agent with a better safety profile, is associated with less risk of hypertonic uterine action, fetal distress and caesarian section while headache, increased oxytocin requirement and hypotension are more likely to occur with the former.

INTRODUCTION
Induction of labor is indicated when the risks to either the mother or the fetus of continuing the pregnancy outweigh the benefits. The conditions which commonly necessitate induction of labor include preeclampsia, postdatism, prelabor rupture of membranes, maternal medical disorders, fetal growth restriction and intrauterine fetal demise (Hibbard *et al.*, 1998). The success of labor induction largely depends on the `favourability' of cervix. Various methods like insertion of extra amniotic self retaining catheter, hygroscopic cervical dilators and prostaglandins have been tried in an effort to ripen the cervix prior to induction (Hibbard 1998, Vengalil 1998, Owen 1991). Prostaglandin E2 or dinoprostone administered intracervically, has been shown to improve bishop score and induction to delivery times in comparison to untreated controls (Owen 1991). However, use of prostaglandins is associated with

complications like uterine tachysystole and rupture of uterus and fetal cardiac rhythm abnormalities (Keller 1984, Vaisanen 2003). Besides, more caution is advocated when these agents are used in women with a scarred uterus.

Nitric oxide (NO) has been recently postulated to have a regulatory role in the myometrium and cervix during pregnancy and parturition, and an endogenous NO system is documented in the human cervix.[6] The present study was planned to evaluate the effects of NO donor isosorbide dinitrate (IDN) on cervical ripening at term, to compare its efficacy and safety with that of dinoprostone gel and to evaluate the maternal and fetal outcome after use of these agents for cervical priming.

MATERIALS AND METHODS

This prospective study was carried out on 100 primigravid women with singleton live pregnancy (between 37 to 42 weeks of gestation) and an unfavorable cervix (modified Bishop score of 0-5), posted for induction of labour during the period between January 2006 to January 2008, in the Department of Obstetrics and Gynaecology at a tertiary care referral centre of India. Women with malpresentations, multiple pregnancy and those with history of epilepsy or bronchial asthma were excluded from the study.

After a thorough history, general physical and obstetric examination (including assessment of Bishop score) all women underwent ultrasonography and Doppler umbilical artery scan for baseline indices. Randomization was done by asking the woman to pick up a slip from a box that contained 50 closed slips of IDN and 50 of dinoprostone. At this time, neither the clinician nor the woman was aware of what ripening agent would be used. Women receiving IDN were assigned to group I while those of dinoprostone were included in group II. Women of group I were administered 40 mg IDN vaginally while those of group II received dinoprostone gel (0.5 mg in 3 gm base) intracervically which was repeated after 6 hours, if the bishop score remained below 6. A repeat umbilical artery Doppler scan was done after 6 hours to know the effect of the drug on fetal circulation while Bishop score was reassessed after 6 and 12 hours. Oxytocin was started after 12 hours in both groups, if required. EFM was used once patient started getting uterine contractions. Abnormal FHR patterns included rates <100, >180, sinusoidal pattern, atypical variable or late decelerations lasting >30 min. Thick or tenacious dark green or black meconium in liquor or clamps of meconium in liquor was taken as evidence of fetal distress. Success of induction was defined as establishment of good uterine contractions within 12 hours and vaginal delivery within 24 hours of the instillation of the first dose of the ripening agent.

All women were monitored for pulse rate, blood pressure, fetal heart rate, uterine contractions, any adverse effects and maternal and neonatal outcome. The clinicians and the women were asked to describe their experience with use of the ripening agent.

RESULTS

The majority of women (39 in group I and 38 in group II) in the study were in the age group of 20-24 years, the mean age being 22.52±2.29 years ad 22.38±2.51 years in group I and II, respectively. A total of 39 (78%) women in group I and 38 (76%) in group II were between 38-42 weeks of gestation, the remaining being at 37 weeks. Preeclampsia and postdated pregnancy accounted for maximum number of inductions (74% in each group) followed by Rh isoimmunization (20% in group I and 18% in group II). Six percent women in the study were induced for fetal growth restriction, decreased fetal movements, oligohydramnios or maternal medical disorders.

6 and 12 hours of drug administration. Table 1 shows the change in bishop score in the study. The change in bishop score after 6 hours of instillation of the ripening agent in both groups was very significant ($p<0.001$). In group II, 80% (24 out of 30) women with an initial score of 0-3 and 20% (4 out of 20) of those with initial score of 4-5 needed a repeat dose of dinoprostone.
Table 2 depicts the success of induction in the present study. A total of 9 women of group I and 13 of group II delivered by the end of 12 hours. However, by 24 hours, 38 women of group I had delivered as

Table 1: Showing change in Bishop scores in the study.

Group	Number of cases	Initial Bishop Score	Mean Bishop Score		
			0 hour	6 hours	12 hours
I	One	0-3 (n=27)	2.556±0.641	4.63±2.115	7.077±2.813
		4-5 (n=23)	4.478±0.511	7.227±2.159	8.267±2.764
II	One	0-3 (n=6)	2.333±0.816	6.167±2.927	8.50±0.707
		405 (n=16)	4.437±0.512	8.267±2.086	10.2±1.789
	Two	0-3 (n=24)	2.522±0.593	4.042±1.197	6.611±1.577
		4-5 (n=04)	4.25±0.500	4.75±0.500	7.5±2.646

The mean bishop score at entry was 3.44±1.23 in group I and 3.20±1.19 in group II, with 27 (54%) women of group I and 30 (60%) of group II having an initial score of 0-3. The score was reassessed after

compared to 31 of group II. Bishop score appeared to be an important predictor for induction to delivery interval in the study. Of the women with an initial score of 0-3, only 3.71% (1 patient) from group I and 16.67% (5 patients) from group I delivered vaginally within 12 hours. While 66.67% (18 patients) of women with an initial bishop score of 0-3 delivered between 12-24 hours in group I, only 40% (12 women) did so in group II. Of the women with bishop score of 4-5, 34.78% (8 women) women of group I and 40% (8 women) of groupie delivered in the first 12 hours and another 47.83% (11 women) and 30% (6 patients) woman delivered between 12-24 hours in group I and II, respectively. The mean induction to delivery interval was 17.99±7.05 hours in group I and 16.68±8.47 hours in group II ($p>0.05$). When analysed in respect to number of doses of dinoprostone used, this interval was 11.77±4.7 hours with a single dose and 21.09±8.75 hours with 2 doses. Oxytocin was required in (38 of group I and 33 of group II) women in the study. Conversely, total of 12 and 17 women in group I and II respectively, did not require any oxytocin supplementation. Out of the 17 cases of group II who did not need oxytocin supplementation, 9 women had received a repeat dose of dinoprostone. Twenty two women of group I and 14 of group II required more than 20 mu/min of oxytocin ($p>0.05$). While majority (38 in group I and 31 in group II) of patients had spontaneous vaginal delivery, 7 women of group I and 12 of group II underwent cesarean section while four women (8%) of each group had instrumental delivery. Fetal distress formed the indication of CS for 11 (out of 12) patients of group II and 4 (out of 7) patients of group I ($p<0.05$). Three patients of group I and one of group II underwent abdominal delivery for failed induction.

Table 2: Showing success of induction in the study

Group	Number of Cases Induced Successfully		Mean Induction Delivery Interval
	Bishop score 0-3	Bishop score 4-5	
I	19/27 (70.37%)	19/23 (82.60%)	17.99±7.05 hours
II	16/30 (53.33%)	15/20 (75%)	16.68±8.47 hours

The mean increase in pulse rate at the end of 2 hours was 11.52±4.86 beats per minute (bpm) and 2.54±4.63 bpm in group I and group II respectively ($p<0.001$). A mean fall of 10.64±7.31 mmHg was observed in systolic blood pressure in group I as compared to a rise by 2.12±12.05 mmHg in group II ($p<0.001$). Similarly diastolic blood pressure fell by 7.32±5.61 mmHg in group I whereas a mean increase in diastolic blood pressure of 2.9±7.47 mmHg was observed in group II ($p <0.001$). There was a mean fall of 0.0077±0.260 and a mean increase of 0.033±0.09 in the resistance index (RI) of umbilical artery in group I and II, respectively. A small insignificant rise in the pulsatility index (PI) of this vessel was noted in the 2 groups.

Headache was the most common adverse effect observed in group I 15 women (30%) as compared to 6 women (12%) in group II, $p <0.05$). Hypertension / dizziness and palpitations were observed in 2 and 4 women (8%) of patients, respectively, in group I. seven women of group II complained of abdominal pain and 2 women of this group had uterine hyperstimulation, in comparison to none from group I. Two women of group I had atonic postpartum hemorrhage (PPH), one during a cesarean section and the other immediately follwing vaginal delivery. The cesarean woman required B-lynch sutures while the other could be managed with uterotonic agents. One woman of group I and 2 of group II had cervical tears.

All woman exhibiting signs of fetal distress (abnormal fetal heart rate patterns or significant MSL) were initially managed by left lateral positioning, stopping oxytocin if it was being given and infusing crystalloid solution in case of maternal hypertension).

Abnormal fetal heart rate patterns were observed in one (2%) and 15 (30%) women of group I and II, respectively ($p<0.001$). One woman of group I and 10 from group II had late decelerations. Three women had variable and 2 had early decelerations in group II. The solitary woman with late deceleration in group I and 8 out of 10 with this feature in group II necessitated abdominal delivery while the remaining 2 had instrumental births. Passage of thick dark green meconium occurred in 4 (8%) women of group I and 11 (22%) of group II ($p <0.05$). Three out of the 4 women in group I with thick meconium delivered with the aid of ventouse while in group II, 4 out of the 11 women with meconium delivered spontaneously, 6 also had abnormal fetal heart rate patterns and had cesarean sections. One woman was detected to have thick meconium stained liquor after 5 hours of instillation of dinoprostone and was also delivered abdominally. None of the babies required admission to intensive care unit.

IMN 140 mg was administered vaginally to women of group I while those of group II received dinoprostone gel intracervically. The clinicians reported no difficulty in vaginal administration of IDN tablets to the women of group I while the instillation of dinoprostone gel was relatively more difficult in 12 (24%) women of group II.

DISCUSSION

Prostaglandins have been used for cervical ripening and induction of labor in the past. They have been shown to reduce cervical resistance by reorganizing the collagen fibrils in the cervix. Administration of prostaglandin E2 (PGE2) causes a decrease in concentration of sulfated glycosaminoglycan (GAG) which in turn reduces electrostatic interactions to result in weakening of the interfibrillary network of the cervix (Dailey 2008). In addition to this, prostaglandins also initiate contractions in the myometrium.

Nitric oxide (NO) is one of the agents that has been postulated to play an important role in conditioning of the uterus and cervix in preparation for labor (Garfield 1998). In concert with progesterone, NO inhibits uterine contractility during pregnancy. At term, production of NO by the uterus and placenta declines and this has been postulated to allow labor to start and progress. In contrast, the NO concentration in the cervix increases at the end of pregnancy and this may be the final pathway for stimulating cervical ripening by activation of metalloenzymes and increased expression of cyclooxygenase (Garfield 1998, Bullarbo 2007).

IDN, the NO donor used in this study is marketed in tablet formulation and is stable at room temperature even in temperate climates. Dinoprostone is available as a gel form and is intended for vaginal / intracervical use.

Induction of labor is commonly required for maternal or fetal indications and a cervical ripening agent can play an important role in its success. The two groups in this study were comparable in terms of age, period of gestation, initial bishop score and indications for induction. Osman *et al.,* (2006) conducted a randomized comparison of PGE2 gel 2 mg per vaginum with the NO donor isosorbide mononitrate (IMN) 40 mg per vaginum for cervical ripening at term and reported a mean change in bishop score of 1.36±1.26 with IMN and 2.29±1.74 for PGE2. Most women in group I in the present study showed improvement in bishop score but this was even better in group II, irrespective of initial score. A better labour outcome with more favorable cervix is evident from table I. Besides the apparent lack of significance could be due to the small number of cases in the study. The relative better result could be due to additional NO donor i.e. IDN in comparison to IMN.

A shortened induction to delivery interval has been reported with PGE2 and NO donors by various authors (Chanrachakul 2000, Nicoll 2001). Our study suggests that in the presence of poor bishop score, dinoprostone causes faster improvement in cervical ripening and uterine activity as compared to isosorbide dinitrate in the first 12 hours. However, when analysed after 24 hours, more number of women successfully delivered per vaginum (76% in group I as compared to 62% in group II). It may thus be inferred that isosorbide dinitrate causes better ripening of cervix and when oxytocin was used after 12 hours, more women delivered vaginally. This is in contrast to group II where dinoprostone caused more uterine contractile activity and more deliveries at 12 hours than in group I. However, lesser number of women (36%) delivered between 12-24 hours in group II than in group I (58%), thus reflecting the declining uterine contractility in group II after the passage of initial 12 hours. In contrast, a good priming effect on cervix in group I may have resulted in more number of deliveries after oxytocin was started after 12 hours.

Most studies have reported 31-64% incidence of spontaneous vaginal deliveries and 18-35% incidence of cesarean section with use of NO donors and PGE2.[10,11] The incidence of vaginal deliveries in our study is comparable. The cesarean section rates of our study are comparable to those in PRIM study for PGE2 group(Osman 2006). However, the lower cesarean section rate for group I (14%) could be due to the use of IDN instead of IMN in the same dose (40 mg), with IDN releasing 2 molecules of NO instead of 1 in case of IMN. In the present study, the initial bishop score was not found to have a significant effect on the outcome in the two groups. However, when the indications for cesarean sections were analysed, it was found that 8% women in group I and 22% in group II had the abdominal delivery for fetal distress ($p<0.05$). Failed induction led to the cesarean section in 6% women of group I and 2% of group II ($p>0.05$). Thus, the incidence of fetal distress was more with the use of PGE2, thus necessitating early delivery in comparison to IDN. The observation that not only lesser number of women of group II needed oxytocin but also required lesser doses of it could be related to the contraction, inducing property of dinoprostone in the myometrium. The smooth in relaxation property of on the other hand, NO donors may predispose to higher oxytocin requirement.

A significant higher increase in pulse rate and fall in blood pressure seen with IDN may be the result of vasodilatation induced by it. Headache, probably the consequence of cerebral vessel dilation, was more common with use of IDN in our study. In the study by Nicoll *et al.,* (2001), headache occurred in 9 out of

13 women who received 20 mg IMN and in 10 of 11 women who received 40 mg IMN and in only 1 women out of 12 who were only examined vaginally (no treatment group), thus implying that increasing the dose of NO donor would probably increase the adverse effect. In present study, 14% women of group II complained of abdominal pain following dinoprostone instillation while no such effect was observed in group I ($p<0.01$). Besides two cases (4%) of uterine hyperactivity were seen in group II. This may be result of contraction inducing property of dinoprostone. This effect of dinoprostone may not only be responsible for the hypertonicity of uterus but also for more fetal cardiac rhythm abnormalities and passage of thick meconium seen in the present study. In the PRIM study (2006), there were 13 women with abnormal fetal heart rate patterns in PGE2 group, as compared to none in IMN group ($p=0.0002$). Six of the 13 women required cesarean delivery for fetal distress in that study. No significant effect, as was the case in the present study, on the umbilical artery indices has been reported in literature(Osman 2006, Nicoll 2001). Hypotension and atonic postpartum hemorrhage (PPH) was more often evident in group I of our study while traumatic PPH occurred more frequently in group II, which again may be the consequence of different modes of action of the two agents. Nicoll *et al.,* (2001) did not report any excess blood loss with use of IMN. However, traumatic complications have been reported to be more common with use of progstaglandins. IDN, by relaxing the uterine smooth muscle may predispose to atonicity of uterus. This smooth muscle relaxation induces by IDN led to a fall of systolic blood pressure by a mean of 10mmHg and the severe atonic PPH that occurred in one patient of group I.

In conclusion, both IDN and dinoprostone appear to be effective agents for cervical ripening. IDN promotes the cervical ripening at term without causing serious clinical maternal and fetal adverse effects. It causes slow ripening of cervix which in the presence of uterine contractile activity leads to spontaneous vaginal delivery within 24 hours. This is in contrast to dinoprostone which initiates uterine contractions, in addition to ripening the cervix, soon after administration and results in more vaginal deliveries at 12 hours in comparison to IDN. However, dinoprostone use is associated with higher incidence of fetal distress and hence increased chances of abdominal delivery. In contrast to PGE2, IDN by itself does not stimulate uterine contractions but predisposes to higher oxytocin requirement, hypotension and atonic PPH. A relatively easier route of administration, better safety profile, easy storability even in temperate climates make IDN an effective alternative to dinoprostone for cervical ripening prior to induction of labor.

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